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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,504	10/18/2000	Frederic DeSauvage	P1748R1	6723

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/17/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/692,504	Applicant(s) DESAUVAGE ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *6-10 and 14-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/29/02 (Paper No. 13), is acknowledged. Claims 1-34 are pending.

Claims 6-10 and 14-34 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-5 and 11-13 *are under consideration in the instant application.*

2. This Office Action will be in response to applicant's arguments, filed 11/29/02 (Paper No. 13). The rejections of record can be found in the previous Office Action (Paper No. 11).

Drawings

3. The drawings submitted 11/29/02 have been approved by the Draftsman.

IDS

4. Applicant's IDS, filed 11/29/02 (Paper No. 15) is acknowledged. The citation provided for the retrieval of search results for "TCCR" has been modified to include the URL, as per MPEP 7-7.05(e).

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claims 1-5 and 11-13 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 11-13 are indefinite in that they utilize an arbitrary protein name, "TCCR". The instant recitation fails to distinctly claim what protein is antagonized. For example, others in the field may isolate the same protein and give it an entirely different name. Sprecher et al. (Biochem. Biophys. Res. Com. 1998; 246:82-90, IDS #57) describe proteins that share identical amino acid sequences as the instant human and mouse "TCCR" proteins, but name the proteins "WSX-1".

Applicant has argued in the response filed 11/29/02 that the term "TCCR" is specifically defined in the specification on pages 14-17 and that some characteristics of the receptor are provided on page 86 at lines 1-33. Applicant further argues that entry of the term "TCCR" into the NCBI protein database results in a listing that includes both the instant TCCR term and the "WSX-1" term.

Applicant's arguments have been fully considered but have not been found convincing for the reasons of record. The "definition" provided on pages 14-17 of the specification is so ambiguous as to be meaningless, encompassing not only the TCCR polypeptides of SEQ ID NOS:1 and 2, but also variant sequences which comprise fragments as small as 10 amino acids and have only 80% identity.

In addition, while the NCBI database search retrieved by Applicant on 11/25/02 does recognize the term "TCCR", the effective filing date of the instant application is 10/20/99. Applicant provides no information to establish that "TCCR" was an art-recognized term at the time of the instant applications effective filing date.

Thus the term "TCCR" as set forth in the instant application is ambiguous, and the term was not an art-recognized term at the time of filing.

The rejection is maintained.

Applicant should particularly point out and distinctly claim the "TCCR" by claiming a sufficient number of characteristics associated with the protein (e.g. amino acid sequences).

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. It is again noted that while the instant claims were limited by the restriction requirement to methods in which the "TCCR antagonist" is an antibody to TCCR; the breadth of the claims encompassing any "TCCR antagonist" is also addressed under 35 USC 112, first paragraph, in the rejections set forth below.

9. Claims 1-5 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's arguments, filed 11/29/02, have been fully considered but have not been found convincing for the reasons of record.

The rejection of record may be found in full in Paper No. 11.

Applicant argues that representative structures of TCCR have been provided in Figures 3-5 and pages 32-33 and 86 of the specification, and that functions of TCCR have been provided using a knockout mouse model in the Examples.

Applicant further argues that given the structure and function of TCCR, and screening assays as set forth on pages 59-60 and pages 104-106 of the specification, Applicant is in possession of antagonists of TCCR function that are at least antibodies to TCCR and antisense molecules.

However, the Examiner maintains that Applicant has not provided a sufficient written description of any structure that may be correlated with the desired antagonistic function.

In the instant case a "TCCR antagonist" for use in the instant methods is simply an indication what the material does, not of what it is.

While acknowledging that antibodies to TCCR and antisense molecules are described in the specification, the claims are not limited to antibody and antisense antagonists. Rather, the claims are drawn to an extensive genus that is defined solely in terms of function, i.e., antagonizing TCCR function. A "TCCR antagonist" encompasses *any* molecule with the functional activity of stimulating the differentiation of T cells into a Th2 subtype, or treating a Th1-mediated disease. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed in view of the description of two species of antagonists.

Applicant's attention is directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

The rejection is maintained.

Applicant is again directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claims 1-5 and 11-13 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments, filed 11/29/02, have been fully considered but have not been found convincing for the reasons of record.

The rejection of record may be found in full in Paper No. 11.

Applicant's arguments are addressed below in the context of a reiteration of the rejection of record.

The Examiner has previously provided reasons why the specification does not appear to provide a sufficient enabling description of the instant methods of enhancing the differentiation of T-cells into the Th2 subtype, or of treating a Th1-mediated disorder.

The specification discloses that mice in which the gene encoding the TCCR polypeptide as set forth in SEQ ID NO:4 has been inactivated ("TCCR Knockout mice", Examples 1-2 on pages 86-88) demonstrate increased lymphocyte infiltration into the lungs compared to wild-type mice in a mouse model of asthma (example 3 on pages 89-91), have reduced production of immunoglobulin isotypes associated with Th1 responses in response to antigenic challenge (Example 12, pages 103-105), and have decreased ability to clear infections requiring a Th1 response (page 105). In addition, the specification discloses that T cells from TCCR knock out mice exhibit decreased Th1 and increased Th2 cytokine production in in vitro differentiation assays (page 105).

As previously noted, the state of the art recognized that it is unpredictable as to whether information derived solely from gene inactivation in mice is indicative that the protein inactivated is directly responsible for the observed phenotype.

Mak et al. (Nat. Rev. Immunol. 2001; 1:11-19, of record) review that although gene-targeting has provided great insights into gene function, there are caveats that must be considered when assessing the phenotypes of genetically engineered mice (see entire reference, but especially the bridging paragraph of pages 13 and 14). In particular, Mak et al. note that engineered mutations in one gene can affect the expression of unaltered neighboring genes, giving rise to phenotypes that are unconnected to the gene of interest; and that gene deletions can also affect the architecture of an organ, such as the lymph nodes or spleen, which would have secondary effects on cells within these organs. Mak et al. conclude that there is a danger that such effects might be misinterpreted as primary effects of the gene mutation on the cells themselves.

Applicant has argued that Huhtaniemi et al. (Mol. Cell Endocrin, 2002; 187(1-2):49-56, IDS) and Stewert et al. (Nature 1992; 359(6390):76-79, IDS) provide evidence that knockout mice can be used to provide evidence of a function of the knockedout gene. Applicant further asserts that the Examiner has failed to explain why the concerns of Mak et al. apply to the TCCR knockout mouse.

As reiterated supra, the concerns of Mak et al. apply to *any* knockout mouse because they point out that the observed phenotype is due to a highly complex in vivo environment that, without further supporting experiments, fails to establish a primary effect of the knockout gene. Applicant does not appear to have provided any additional supporting experiments such as the inhibition of TCCR activity in a mouse which did express TCCR throughout its development.

The Examiner has been unable to identify any post-filing date references which corroborate the observations made in TCCR knockout mice or cells derived therefrom. In the absence of such supporting objective evidence, e.g., data provided by applicant in a Declaration or post-filing date references; the Examiner maintains that it is unpredictable if the phenotype observed in the TCCR knockout mouse is due to direct inactivation of TCCR. It would require undue experimentation of the skilled artisan to establish that the phenotype observed in the TCCR knockout mouse was a direct consequence of inactivation of the gene encoding TCCR, and in the absence of such objective evidence the application of TCCR antagonists in the instantly recited methods would be highly unpredictable.

Further, the Examiner maintains that the breadth of the antagonists encompassed by the instant claims is extensive, particularly since "TCCR" is an indefinite term, not limited to the polypeptides of SEQ ID NO:2 and SEQ ID NO:4. Even if a direct role of the TCCRs comprising SEQ ID NO:2 or SEQ ID NO:4 were established by sufficient objective evidence, the specification still would not provide a sufficiently enabling description of how to make and use "TCCR antagonists" commensurate in scope with instant claims 1-5.

Applicant argues that the specification provides sufficient guidance as to how to make and use TCCR antagonists because it provides screening assays and because the production of antagonists that are antibodies and antisense molecules was well known in the art.

Although the specification does set forth generalized approaches for rational drug design and drug screening (Examples 10 and 11 on pages 101-103), as previously noted the skilled artisan was well aware that the design of small molecule antagonists of cytokine receptors such a TCCR was a formidable task. As noted by Proudfoot et al. (Immunol. Rev. 2000; 177:246-256, of record), although small molecule antagonists have been produced for receptors of the chemotactic cytokines known as chemokines, no antagonists of cytokine receptors have yet been produced, despite intensive investigations (see especially comment bridging columns 1 and 2 on page 253).

Thus although the specification provides sufficient guidance as to how to make certain antagonists of the TCCR polypeptides of SEQ ID NO:2 and SEQ ID NO:4, such as the antagonists antibodies recited in claims 11-13; it would require undue experimentation of the skilled artisan to make a representative number of "TCCR antagonists" commensurate in scope with instant claims 1-5, which encompass any molecule with the function of antagonizing TCCR by any mechanism.

Such a recitation is claiming in terms of function. However, "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

In addition to the uncertainty associated with production of "TCCR antagonists", it would also be unpredictable as to whether a "TCCR antagonist" could be used to accomplish the instantly recited methods, particularly *in vivo*.

It is again noted that instant claims 1-5 encompass a multitude of structurally diverse molecules. However, *in vivo* application of these various "TCCR antagonists" is fraught with technical difficulties, even were such antagonists developed, as noted previously.

Given the technical difficulties associated with *in vivo* therapies in general, the limited guidance provided in the specification and the breadth of the claims encompassing any antagonist of any "TCCR"; the skilled artisan would be faced with undue experimentation in determining which "TCCR antagonists" could be utilized *in vivo*. Thus the skilled artisan would be forced to conduct undue experimentation to determine which, if any, antagonists of TCCR would function in the instant methods.

Applicant has argued that in vivo data is not required when in vitro data can be provided that can be reasonably correlated to the in vivo animal model, citing In re Brana, 51 F3d 1560 (Fed. Cir. 1975). Applicant points to in vitro results observed with cells (page 105 of the specification), argues that these results correlate with an in vivo phenotype, and concludes that in vitro results should be sufficient in the instant case.

The Examiner acknowledges that there are instance when in vitro models may be sufficiently well characterized such that they are predictive of in vivo function of an antagonist shown to work in the in vitro system.

However, as noted supra the state of the art indicated that an observed phenotype in a knockout mouse was due to a highly complex in vivo environment that, without further supporting experiments, fails to establish a primary effect of the knockout gene. Supporting experiments appear to be lacking in the instant case. This contrasts with the knockout mouse models of Huhtaniemi et al. and Stewert et al., again pointed to by Applicant, each of which address molecular pathways for which abundant additional data was available.

It is also noted that the experiment pointed to by Applicant on page 105 of the specification provides in vitro data that cells from the knockout mice fail to differentiate into TH1 type cells. These data do not show that any particular antagonist works in an in vitro system, which might then be a basis for asserting predictability regarding an in vivo effect.

Thus contrary to Applicant's assertions, the instant in vitro experiments further characterizing the cells from knockout mice rather evaluating the in vitro effect of an added antagonist do not appear to provide a sufficiently well-characterized system to support in vivo function of any particular antagonist. Rather, they provide a starting point requiring extensive and undue further experimentation.

Applicant further argues that certain antagonists, such as antibodies, are well characterized with respect to in vivo application, and that the Examiner has failed to provide any technical reasons why these antagonists would not function in vivo.

The comments regarding the general unpredictability of in vivo therapies were made with respect to the breadth of antagonists encompassed by the instant claims and is maintained as set forth supra.

Further, while the Examiner acknowledges that in vivo application of antibodies is not subject to the same level of uncertainty associated with other molecules, the Examiner reiterates that there is insufficient objective evidence of record that an antibody antagonist of TCCR would result in the same in vivo phenotype as observed with the knockout mouse, for the reasons set forth supra.

Finally, claims 3-5 and 11-13 recite methods of treating Th1-mediated diseases by administering a TCCR antagonist, including treating autoimmune inflammatory diseases, such as inflammatory bowel disease, and allograft rejection. Autoimmune inflammatory diseases that are Th1-mediated encompass a highly diverse group of diseases involving distinct pathophysiologies.

Applicant again argues that sufficient in vitro data has been provided to enable the instant method of treating the diverse diseases encompassed by the instant claims.

Applicant's comments regarding the predictive value of the instant in vitro data has been addressed supra. Further, it is again noted that, as reviewed by O'Shea et al. (Nat. Rev. Immunol. 2002; 2:37-45, of record) the state of the art recognized that the role of cytokines in regulating T-cell subtype for these diseases was extremely complicated: cytokines involved in determining T-cell subtype were known to be pleiotropic, exhibit functional redundancies, be involved in complex feedback loops, and to have both immunostimulatory and immunosuppressive activities (see especially pages 37-38).

In addition to this complexity associated with cytokines and T-cell subtype, it is noted that for at least the autoimmune inflammatory disease insulin-dependent diabetes mellitus, treatment is in general limited to animals in which later development of the disease can be predicted. In humans, the immune system has already destroyed the beta cells which produce insulin by the time a patient presents with the symptoms of insulin-dependent diabetes mellitus. Thus in the absence of detailed protocols to detect the autoimmune inflammatory disease before beta cell destruction occurs, the specification does not appear to enable a method of treating insulin-dependent diabetes mellitus.

For these reasons the Examiner maintains that data obtained solely from a TCCR knockout mouse model in which the polypeptide of SEQ ID NO:4 has been inactivated does not appear to provide sufficient guidance as to how a "TCCR antagonist" would function in a method of enhancing the differentiation of T-cells into the Th2 subtype, or of treating a Th1-mediated disorder in general, and human insulin-dependent diabetes mellitus in particular. No working examples are provided with respect to the ability of any antagonist in general, or a monoclonal antibody antagonist in particular, to produce modifications of T cell responses in mice in which the TCCR molecule is expressed. Further, no working examples are provided with respect to the effects of any antagonist of TCCR in general, or a monoclonal antibody antagonist of TCCR in particular, to mediate any effect with respect to human T cells. Finally, the specification does not appear to provide sufficient objective evidence that a "Th1-mediated disease", including inflammatory bowel disease, may be treated by administering any TCCR antagonist in general, or a monoclonal antibody antagonist of TCCR in particular.

Applicant is again invited to provide sufficient objective evidence supporting that antagonists of TCCR, in particular monoclonal antibody antagonists, do function to enhance differentiation of T-cells into the Th2 subtype. Similarly, Applicant is invited to provide sufficient objective evidence that monoclonal antibody antagonists of TCCR inhibit one or more disease that is a "Th1-mediated disease".

However, given the unpredictability associated with the model and data disclosed; the experimentation left to one skilled in the art to practice the claimed invention is unnecessarily, and improperly, extensive and undue.

The rejection is maintained.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. This application contains claims 6-10 and 14-34 drawn to an invention nonelected with traverse based on an incomplete response in Paper No. 10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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March 17, 2003

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